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EDITORIAL

REACTIONS TO THERAPY FOR VENEREAL DISEASES

The reactions of the host to therapeutic agents have always been of prime concern to the venereologist. Both the host and the invading organisms may react to the new environment created by therapeutic substances and, ideally, the drugs used should be lethal to the responsible organisms within the tissues of the patient without harming the tissues themselves.

In bygone years, excessive salivation, due to the toxic action of mercurials, was mistakenly regarded as an index of successful therapy and jars for measuring the quantity of saliva are now museum objects of historical interest. Although mercury was widely used for centuries, some physicians considered that its benefit to the sufferer from syphilis was offset by its toxic effects. Indeed, late in the 19th century, Boeck, of Oslo, believing that his patients were better off without it, declined to use mercury—thus creating the famous Bruusgaard material which later made possible the valuable Oslo Study on the outcome of untreated syphilis.

In the arsenical era the margin between destruction of the treponeme and toxicity to the patient was still closer than desired—a fact perhaps more appreciated in retrospect than at the time. The pentavalent arsenical preparations caused optic atrophy and the trivalent "magic bullets" were not always well tolerated by the patient; it is said that immediately after the first world war, if a policeman found a vomiting person lying in the gutter within one mile of Piccadilly Circus, London, the sufferer was not put in charge for drunkenness but taken to the Lock Hospital in Dean Street. The ninth-day erythemas, exfoliative dermatitis, encephalitis, agranulocytosis, and other haemopoietic complications, the sometimes severe stomatitis associated with bismuth therapy, and the syringe-transmitted hepatitis which might affect up to one half of the patients under treatment for syphilis in some hospitals, made arsenical and bismuth therapy a hazardous procedure. The sulphonamides, too, brought new problems of toxicity, including upset to skin and blood and anuria due to crystallization of the drug in the urinary tract. With the early preparations minor toxic complications were frequent. Headache and malaise were commonplace and cyanotic people seen in the street were more likely to be sufferers from gonorrhoea and its treatment than from congenital heart disease. Eggs and onions (probably mistakenly) became forbidden foods for patients with gonorrhoea and were added to the earlier list which included alcohol, spices, and peppers.

The three decades before 1945 were thus years of chemotherapy and toxicity. An entirely new era—the era of antibiotics—dawned during the second world war when penicillin became available for the casualties, both medical and surgical, of the Allied armies. From penicillin, too, has stemmed the discovery of other potent antibiotics. The feature of these remedies—in comparison with the effective drugs of previous decades—has been their extremely low toxicity. Penicillin, particularly, is remarkable in this respect. It has been estimated that the single 50 per cent. lethal dose in man is in the region of 25 to 150 million units (Guthe, Idsöe, and Willcox, 1958)—a dose almost beyond the physical capacity of the physician to administer. This antibiotic era is one in which effective therapy has been accompanied by extremely little toxicity in the quantitative sense (*i.e.* assuming all persons will exhibit toxic reactions to drugs if a sufficient quantity is given). This notwithstanding, important new problems have arisen and reactions to antibiotics are now recognized to be complex and increasingly frequent. Reactions to penicillin, the antibiotic most used so far, have been extensively reviewed in the *Bulletin of the World Health Organization* by Guthe, Idsöe, and Willcox (1958) and a careful study of this monograph is recommended. In this issue (page 208) Willcox also summarizes the leading facts.

The most serious side-reactions of penicillin are *allergic* in nature, depending on the acquired sensitivity of the patient rather than on any basic toxicity of the antibiotic itself. The effects are qualitative rather than quantitative, as very small amounts of the drug cause upset in susceptible persons only. To the mild urticaria and occasionally severe sensitization dermatitis and angio-oedema—complications observed since the earliest days of penicillin usage—has been added anaphylactic shock in an increasing number of cases, many of which have proved fatal. This increase in allergic reactions has followed the extensive use of antibiotics and in the USA it is estimated that over 1,000 deaths from penicillin have already occurred (Peters, Henderson, and Prickman, 1957). Anaphylaxis is of importance not only to the patient, who may lose his life, especially when penicillin has been given for some trivial condition, but also to the doctor to whom it may represent a serious legal hazard. In New York City, for example, of thirty known cases of anaphylaxis to penicillin, nine are, or have been, the subject of legal proceedings (Rosenthal, 1958). In some countries, too, venereal disease control programmes have been retarded by the publicity given to cases of sudden death immediately following the administration of penicillin.

Happily, in venereal diseases clinics, the reported deaths are few. A recent WHO survey, covering over 600,000 patients treated with penicillin, disclosed only nine deaths or one in over 69,000 cases treated (Willcox, 1958). In a survey of over 16,000 patients treated for venereal disease in the USA the incidence of anaphylactic reactions was only 0·2 per cent. and none died (Smith, Cutler, and Price, 1955). During the recent meeting in London of the International Union against the Venereal Diseases and Treponematoses, Dr. W. J. Brown (USA) presented further data relating to some 39,000 venereal diseases patients treated with repository penicillins; none had died, although there had been an apparent increase in the incidence of reactions through the years. Data from Great Britain are less comprehensive, but Willcox and Fryers (1957) reported reactions observed after 7,300 injections of penicillin given to 895 patients. No unequivocal case of anaphylactic reaction was noted, although one patient died from pneumonia complicating a sensitization dermatitis. Allergic reactions of all sorts were more common in patients receiving multiple injections for syphilis than in patients given one injection for the treatment of gonorrhoea. Morton (1957) reported on 9,382 injections of penicillin given to 403 patients: with 5,870 injections of procaine penicillin given to 256 patients, there were nine instances of anaphylactic reaction, but with 3,512 injections of the long-acting benethamine penicillin given to 147 patients, there was only one such case; all recovered.

Of no less importance, but of less dramatic impact, as their effects may be diffuse and incapable of evaluation until a considerable interval has elapsed (during which time other factors may render evaluation more difficult), are what Guthe, Idsöe, and Willcox (1958) have described as *microbiogenic effects*. Apart from host reactions (*e.g.* therapeutic shock and therapeutic paradox, which may arise from the very effectiveness of antibiotics), the organisms themselves may react to the new environment permitting overgrowth of other bacteria and super-infection with resistant staphylococci and other organisms including monilia may occur. These events may arise not only from organisms already present in the treated patients, in whom resistant strains find an opportunity to flourish when the previously competing sensitive strains have been eliminated, but also from cross-infection in hospitals. Thus Man's recent triumph over infection is now constantly threatened by the adaptation of the organisms to new circumstances.

Discouragement of the indiscriminate use of antibiotics will do much to reduce both host reactions and reactions by invading organisms. In Great Britain antibiotics cannot be bought over the counter, but this is not the case everywhere in the world. Even in Great Britain, as indicated by Willcox in this issue (p. 208), considerable advertising pressure is exerted on doctors to prescribe antibiotics.

Unfortunately no simple and reliable test at present exists to indicate which patients are allergic before each treatment is given. Skin tests may be negative in some patients who subsequently prove sensitive, and positive skin reactions may be seen in persons who may suffer no serious inconvenience when penicillin is given later. Also, as emphasized at the recent WHO Expert Committee on Venereal Diseases and Treponematoses, skin tests may be dangerous in persons already suspected of being sensitive to penicillin and should not be undertaken in such circumstances. The best available method of prevention is to note any history of previous reactions or symptoms which might indicate sensitization; other antibiotics may then be used instead. Finally, the availability of drugs and equipment to treat anaphylactic reactions promptly is of paramount importance, as was recommended over 5 years ago (*Brit. J. vener. Dis.*, 1954), and reiterated at the recent WHO Expert Committee. Whenever penicillin is given, an "anaphylactic kit" containing adrenaline hydrochloride, injectable antihistamine,

and other life-saving drugs, with suitable sterile syringes should always be at hand. The value of penicillinase in anaphylactic reactions has not yet been established but warrants further investigation: some patients, however, may show anaphylaxis to this enzyme itself.

Sensitivity to penicillin, already far from rare, is likely to become more widespread. Serious allergic reactions must be anticipated, especially in syphilitic patients and those treated repeatedly for gonorrhoea. In the USA the fatality rate has dropped since there was a greater awareness of the seriousness of anaphylaxis; in 1953/57 the fatality rate was 9·1 per cent. compared with 28 per cent. in an earlier survey (Welch, Lewis, Weinstein, and Boeckman, 1958). Greater awareness of the danger, close interrogation of the patient before each treatment, and the immediate availability of the "anaphylactic kit" will combine to avoid preventable fatalities. Otherwise, there is real danger that the undoubted blessings of penicillin will be lost and that, in respect of syphilis (and gonorrhoea), the cure may once again prove almost as dangerous as the disease.

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INTERNATIONAL UNION AGAINST THE VENEREAL DISEASES AND THE TREPONEMATOSES

The proceedings of the General Assembly of the International Union Against the Venereal Diseases and the Treponematoses, held in London during October, 1959, will be published in the *British Journal of Venereal Diseases* (issues of March and June, 1960). The papers will be printed in English but will be accompanied by summaries in French.